Antenatal maternal anxiety modulates the BOLD response in 20-year-old men during endogenous cognitive control

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ORIGINAL RESEARCH

Antenatal maternal anxiety modulates the BOLD response in 20-year-old men during endogenous cognitive control

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Abstract

Evidence is building for an association between the level of anxiety experienced by a mother during pregnancy and offspring cognition and structural and functional brain correlates. The current study uses fMRI to examine the association between prenatal exposure to maternal anxiety and brain activity associated with endogenous versus exogenous cognitive control in 20-year-old males. Endogenous cognitive control refers to the ability to generate control over decisions, strategies, conflicting information and so on, from within oneself without external signals, while exogenous control is triggered by external signals. In line with previous results of this long-term follow-up study we found that 20-year-olds of mothers reporting high levels of anxiety during weeks 12–22 of pregnancy exhibited a different pattern of decision making in a Gambling paradigm requiring endogenous cognitive control, compared to adults of mothers reporting low to average levels of anxiety. Moreover, the blood oxygenation level dependent (BOLD) response in a number of prefrontal cortical areas was modulated by the level of antenatal maternal anxiety. In particular, a number of right lateralized clusters including inferior frontal junction, that were modulated in the adults of mothers reporting low to average levels of anxiety during pregnancy by a task manipulation of cognitive control, were not modulated by this manipulation in the adults of mothers reporting high levels of anxiety during pregnancy. These differences in brain functional correlates provide a neurobiological underpinning for the hypothesis of an association between exposure to maternal anxiety in the prenatal life period and a deficit in endogenous cognitive control in early adulthood.

Keywords Neurocognitive tasks · Brain network · Task-related fMRI · Gambling paradigm · Early adversity · Developmental origins of health and disease (DOHaD) · Developmental origins of behavior, health and Disseas (DOBHaD) · Prospective study · Maternal psychological distress · Pregnancy · Adult offspring

Introduction

There is an increasing number of prospective studies revealing evidence for an association between prenatal exposure to maternal distress during pregnancy and negative offspring outcome. Outcomes include delayed motor and cognitive development, negative affectivity and difficult temperament, altered cognitive, behavioral, and affective functioning, and enhanced susceptibility to neurodevelopmental and psychiatric disorders (Bock et al. 2015; Bowers and Yehuda 2016; Lewis et al. 2014; Van den Bergh et al. 2005a, b, 2017; Stein et al. 2014). These studies are part of the study field

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of'Developmental origins of behavior, health and disease' (DOBHaD; Van den Bergh 2011), which is gaining interest within the broader field of 'Developmental Origins of Health and Disease' (DOHaD; e.g., Gluckman et al. 2008; Hanson and Gluckman 2011; Räikkönen et al. 2011) and developmental psychopathology (Van den Bergh et al. 2018). Since maternal distress is potentially preventable, results of DO(B)HaD research bears important implications for preventive mental health care and hence public health policy (e.g., Bauer et al. 2016).

Importantly, in recent years evidence from neuroimaging studies is building for short- and long-term functional and structural brain alterations in offspring exposed to maternal psychological distress during pregnancy (MPDP). These changes are seen as more or less permanent markers of exposure to MPDP, potentially increasing the risk for cognitive, behavioral, and affective deficits and disorders. Prospective studies focusing on brain structure have studied the relationship between MPDP and either grey matter structure (alterations mostly observed are volume and/or cortical thickness reduction in frontal, parietal, temporal, limbic areas and cerebellum) or white matter microstructural changes (alterations involve lower diffusivity in frontal and temporal regions (Buss et al. 2010; Chen et al. 2015; El Marroun et al. 2016; Lebel et al. 2016; Qiu et al. 2013, 2015b; Posner et al. 2016; Rifkin-Graboi et al. 2013, 2015; Sandman et al. 2015; Sarkar et al. 2014; Wen et al. 2017). Functional brain changes were mostly studied with encephalography (EEG). Results showed associations between MPDP and greater relative right frontal EEG (resting state-EEG studies; e.g., Field et al. 2010; Lusby et al. 2016, Soe et al. 2016), or with specific EEG components indicating altered auditory attention/processing and affective picture processing (event- related EEG studies or -event- related potential (ERP) studies: e.g., Harvison et al. 2009; Hunter et al. 2012; Otte et al. 2015; van den Heuvel et al. 2015, 2017). Furthermore, functional MRI studies have reported changes in amygdala-thalamic, amygdala-cortical (e.g. (pre)frontal, cingulate, temporal cortex), and amygdala-subcortical functional connectivity (rs-fMRI studies; e.g., Posner et al. 2016; Qiu et al. 2015a; Scheinost et al. 2016). In addition to the effects of maternal psychological distress itself, treatment of maternal depression with selective serotonin reuptake inhibitors has been shown to be associated with gray matter volume expansion in the right amygdala and increased connectivity between the right amygdala and the right insula in infants with a mean age of 3.40 weeks (Lugo-Candelas et al. 2018). For recent reviews of study design, imaging modalities and results of the studies cited we refer to: Franke et al. 2017; Scheinost et al. 2017; Van den Bergh et al. 2017; Van den Bergh et al. 2018).

The current study involves the oldest prospective cohort and may reveal consistency (and persistence) of effects of MPDP until age 20, with the original sample of pregnant mothers being recruited in 1986 in the University Hospital of Leuven (Belgium). In prior studies of our cohort, high maternal anxiety during pregnancy was related to higher fetal motor activity (as measured with ultrasound) and higher neonatal motor activity (Van den Bergh 1990) and to ADHD symptoms, externalizing problems and anxiety at the age of 8–9 years (Van den Bergh and Marcoen 2004). At the age of 14–15 (Van den Bergh et al. 2005a, 2006) and 17 (Mennes et al. 2006), high maternal anxiety weeks at 12–22 weeks of pregnancy was associated with specific cognitive deficits-i.e., endogenous but not exogenous cognitive control - as measured with a battery of cognitive tasks. Endogenous cognitive control refers to the ability to generate triggers from within oneself (i.e., endogenously) in order to control actions, decisions, strategies and thoughts interfering with optimal task performance. It is opposed to exogenous cognitive control where cognitive control is triggered by external signals (e.g., a sound) (Brass and von Cramon 2004; Miller and Cohen 2001). In a second study in the 17-year-olds, electroencephalography (EEG) was used to measure event-related potentials (ERPs) while the participants were performing a Go/Nogo task measuring exogenous cognitive control and a Gambling paradigm measuring endogenous cognitive control (Mennes et al. 2009). Effects were present in the Gambling paradigm, but not in the GO/Nogo task. Importantly, the dissociation in the effect of antenatal maternal anxiety on exogenous versus endogenous cognitive control was evident in cognitive performance as well as in brain activity.

The aim of the current study is to explore the consistency of long term effects of maternal anxiety on offspring cognition and functional brain correlates in the 20-year-old offspring. More specifically, our study investigates brain correlates underlying the association between maternal anxiety during pregnancy and endogenous cognitive control. Based on the previous results in the same sample (Mennes et al. 2006; Van den Bergh et al. 2005a, 2006) we hypothesized the functional fMRI-observed brain differences to be situated in the prefrontal cortex, and more specifically in orbitofrontal cortex (Mennes et al. 2006). We will investigate the 20-year-olds with the Gambling paradigm used before with ERP in the 17 year olds (Mennes et al. 2009). In this paradigm participants have to assess risks, make decisions, monitor their total scores and deal with gains and losses, all requiring endogenous cognitive control. As the prefrontal cortex and its connected circuitry is regarded the control center for such complex executive behavior, we expect different prefrontal areas to be modulated by this task (Miller and Cohen 2001). In addition, imaging studies using task-switching paradigms identified a region labelled inferior frontal junction, at the junction between inferior frontal sulcus and inferior precentral sulcus, as a key region in endogenous cognitive control, next to mid-dorsolateral prefrontal cortex and medial-frontal regions (Brass et al. 2005; Brass and von Cramon 2004; Forstmann et al. 2005).

To the best of our knowledge, our study sample is the only prospective longitudinal sample in the DO(B)HaD field that includes offspring cognitive ánd multimodal brain imaging measures across adolescence and adulthood. This makes the current study an innovative and important one. However, since our current sample size is limited our results should be regarded as preliminary. As will be explained, the internal validity of our results is sound considering valid data gathering and data analyzing techniques, however external validity will only be guaranteed after the results would have been confirmed in a larger sample.

Methods

Participants

At the start of the study, nulligravidae aged between 18 and 30 years old, who were between 12 and 22 weeks pregnant and without obstetrical complications or medical risks were recruited from the University Hospital Gasthuisberg in Leuven (Belgium). All participating mothers ($N = 86$) were Caucasian, Dutch-speaking and none had a psychiatric history. Medical, pregnancy and birth outcome measures were obtained from hospital records. We refer to previous publications for a broader description of the sample and study design (Van den Bergh and Marcoen 2004; Van den Bergh et al. 2005a; Mennes et al. 2006).

Previous results of the longitudinal research project this study is part of yielded more consistent results in boys compared to girls. This might be due to the fact that the assessed cognitive functions are more likely to be associated with antenatal maternal anxiety in boys, compared to a higher chance for mood-related disorders in girls (Van den Bergh et al. 2008). For this reason and the fact that the high anxiety offspring group comprised only five women, we included only men in the current study.

For the current study, eighteen 20-year-old male participants were selected based on the anxiety grouping at age 17. At that age, the participants were divided in a low-average and high anxiety group based on whether the anxiety scores of their mothers during weeks 12–22 of their pregnancy was lower than 43 (< Pc 75) or at least 43 (> = Pc75) (see Mennes et al. 2006 and see 2.1 below). Ten of these participants were part of the high anxiety group and except for one participant who could not be contacted and one participant who wore braces (i.e., was not MRI compatible), all were included in the high anxiety group of the current study ($n = 8$). The data of the participants in the high anxiety group were compared to those of 10 participants of the low-average anxiety group. The participants of the low-average anxiety group were selected to match the cognitive abilities of those in the high anxiety group. One participant of the low-average anxiety group was excluded from the final analyses because his performance on the gambling task was well outside the range of the other participants in the low-average anxiety group. Therefore, the final low-average anxiety group included nine men compared to eight men in the high anxiety group. Mean Performance IQ (WAIS-III) in the low-average group was 99.67 ($SD = 9.95$), compared to 98.25 ($SD = 8.65$) for the participants in the high anxiety group. This difference was not significant, proving that both groups were appropriately matched (t15 = −.31, $p = .76$).

Participants in both groups were born between 36 and 40 weeks ($M_{\text{High anxiety}} = 39.14$ weeks ($SD = 1.5$), $M_{\text{Low-average anxiety}} = 38.9$ weeks ($SD = 2.17$); t15 = .24, $p = .81$) and 5 min had Apgar scores of 9 or 10. There was no difference in mean birth weight between both groups ($M_{\text{High anxiety=}}$3478 g ($SD =$ 403.54); $M_{\text{Low-average anxiety}} = 3470$ g ($SD = 603.96$), t15 = .03, $p = .97$). The mean age of the participants was 20.07 ($SD = .23$) in offspring of the high anxiety group and 20.00 in the low-average anxiety group ($SD = .21$) (t15 = .553; $p = .52$).

Measures of maternal anxiety during and after pregnancy

Maternal anxiety was measured with a Dutch version of the State Trait Anxiety Inventory (STAI; Van der Van der Ploeg et al. 1980) at least three times during pregnancy (i.e., at 12–22, 23–31 and 32–40 postmenstrual weeks). The STAI contains 2 subscales each consisting of 20 items with a four-point scale (1 to 4). The State subscale provides a valid measure of the intensity of transitory anxiety in response to real life stress. Trait anxiety refers to disposition or proneness to react with anxiety. A cut-off value of 43 was chosen to divide the sample in a low-average versus high anxiety group. This value corresponds with percentile 75 of the State anxiety scale, completed between 12 and 22 weeks of pregnancy in our total sample. Similarly, in a recent population-based study in the Netherlands ($N = 6.443$) 43 was taken as cut-off value for high anxiety measured with the State anxiety subscale for the STAI (Koelewijn et al. 2017). As expected, at 12–22 weeks of pregnancy maternal anxiety was higher in the high anxiety group compared to the low-average anxiety group ($M_{\text{High anxiety}} =$ 51.6 ($SD = 6,00$), $M_{\text{Low-average anxiety}} = 36.48$ weeks ($SD =$ 4.30); t 15 = 6.02, $p = .000$). However, there was no difference in maternal anxiety between the experimental groups at weeks 23–31 ($M_{\text{High anxiety}} = 41.88$ ($SD = 8.98$), $M_{\text{Low-average anxiety}} =$ 36.33 weeks ($SD = 11.13$); t 15 = 1.11, $p = .285$) and weeks 32–40 ($M_{\text{High anxiety}} = 38.67$ weeks ($SD = 9.28$), $M_{\text{Low-average anxiety}} = 38.67$ weeks ($SD = 7.55$); t 15 = .16, $p = .87$).

Because sustained high maternal anxiety in the life course of the offspring may affect offspring development we wanted to establish a measure that could be used to control for its possible influence on the dependent variables. To this end,

the STAI was postnatally completed by the mothers in each wave of the study: i.e., at 1, 10, and 28 weeks (postnatal part of first wave), at 8/9 years (second wave), at 14/15 (third wave) and at 17 years (fourth wave). A principal component analysis was conducted on all postnatal trait anxiety measures (on the complete sample of the longitudinal study). This revealed one component, explaining 65% of the variance in all six measures. A variable consisting of the standardized component score for each mother was used as covariate; it was not significantly different between the two groups ($M_{\text{High anxiety}} = .51$ (SD=. 99), $X_{\text{Low-average anxiety}} = .29$ ($SD = .95$); t 15 = .46, $p = .65$).

Socioeconomic status: parents' educational level

In prior studies on our cohort, socioeconomic status was based on education of both parents (Van den Bergh and Marcoen 2004), since this highly correlated with employment and income and reflects the material, intellectual and other resources to which the offspring is exposed (e.g., Galobardes et al. 2006). Maternal and paternal education was coded on a 4-point scale: (1) secondary education until age 15 (i.e, 9 years); (2) secondary education until age 18 (i.e., 12 years); (3) higher education: bachelor's degree (i.e.,15 years) (4) higher education: master's degree (16–21 years). In the high anxiety group, 50% of mothers and 62,5% of fathers obtained at least a bachelor's degree; in the low-average anxiety group these percentages were 44,4% and 33,3%. A principal component analysis conducted on maternal and paternal educational level yielded one component explaining 85% of the variance. The mean component score was not different between parents of both groups ($X_{\text{High anxiety}} = -.075$; SD = 1.12), $X_{\text{Low-average anxiety}} = -.52$; SD = −1.04; t 15 = .86, p=. 40).

Parents and offspring behavioral problems and psychopathology

We used the Adult Forms for ages 18 to 59 of the Achenbach System of Empirically Based Assessment (ASEBA; Achenbach and Rescorla 2003). The Adult Self- Report (ASR) was completed by the 20-year-olds and the Adult Behavior Checklist (ABCL) was completed by the mothers and fathers to evaluate the behavior of their son. Questions regarding these measures were not part of our research questions, however, to describe differences in the psychiatric profile of the two groups, we tested whether the high and low-average anxiety groups showed differences on the DSM-oriented scales 'Inattention' and 'Hyperactivity-Impulsivity' and on the broadband dimensions of Internalizing and Externalizing problems (cf. Wiggs et al. 2016). Furthermore, all mothers and fathers also evaluated their own behavior by completing the ASR scale. The scores on the DSM-oriented scales and the broadband dimensions of Internalizing and Externalizing problems derived from the ASR scales completed by the parents can be seen as a mixture of a postnatal environmental exposure variable (i.e., to which parental psychopathology have the 20-year-olds postnatally been exposed?) and a proxy variable of genetic endowment. Both kinds of variables are potential confounders and if significant scale differences between both groups would be found, the analyses regarding the main questions should be controlled for these scales. Yet, no differences between the two groups were detected for Inattention and Hyperactivity-Impulsivity, nor for Internalizing or Externalizing problems no matter whether the measures were based on the ASR completed by the 20-year old himself, or on the ABCL and ASR completed by the mother and the father (all p's < .05). (Complete scale scores and results of statistical tests are available from the last author).

Gambling paradigm

A complete description of the Gambling paradigm can be found in Mennes et al. (2008). The same paradigm was used in the current study. Figure 1 shows a stimulus sequence. A two-sided colored bar appeared on the screen. Participants could gamble on the side they thought a token was hidden underneath by pressing a button according to the chosen side. A correct gamble resulted in winning a number of points that was shown above the stimulus bar (ranging from 10 to 100). An incorrect gamble resulted in losing a number of points shown below the bar (ranging from 0 to 100). However, subjects were also given the opportunity to refrain from making a gamble. If participants felt insecure about their decision, or if they found the gain too low or the loss too high, they could choose not to gamble. In that case they just had to wait for the stimulus to disappear. Refraining from gambling always resulted in earning 20 points. All participants received a 100-point credit to start with and were verbally motivated to earn as much points as possible.

Two changes were made to the paradigm to optimize it for use in fMRI. First, in 33% of trials the feedback and total score stimuli were replaced by dummy trials consisting of the gray background screen with a fixation cross in the middle. This was done to avoid a coupling of the BOLD response between the gambling and the outcome stimuli. The dummy trials were randomly mixed with normal feedback trials. Second, the duration of the decision and feedback phase of the trials was randomly jittered in steps of 100 msec. The decision phase lasted between 3800 and 5800 msec. The gambling stimulus itself remained visible for 3500 msec. The length of the feedback phase varied between 2200 and 4800 msec. The feedback stimulus was visible for 900 msec, after an interval of 100 msec the total score was shown for 900 msec.

Four decision trial conditions could be dissociated in this paradigm for analysis purposes. While the whole paradigm requires endogenous cognitive control, we dissociated two

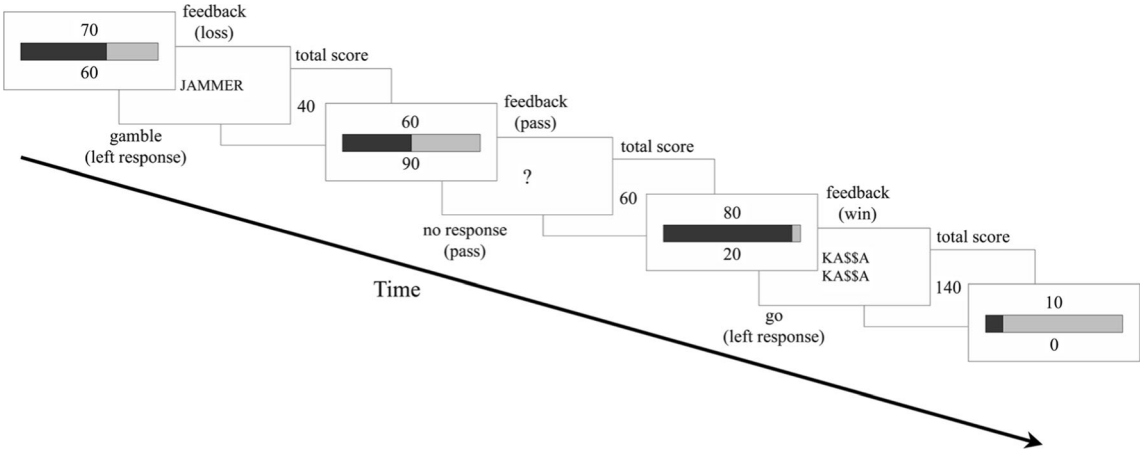

Fig. 1 Stimulus sequence of the Gambling paradigm. (For a full description of the paradigm see Mennes et al. 2008). On each trial participants were shown a proportionally divided colored bar (blue and yellow). Participants could gamble on the location of a hidden token. A correct gamble was rewarded the point shown above the bar, an incorrect gamble resulted in a loss of the points shown below the bar. Participants could also choose not to gamble and settle for a small reward (20 points), as shown in trial 2 of this sequence. After each stimulus bar feedback was given and the total score was updated and shown. (Jammer: Too bad; Ka$$a Ka$$a: 'ka-ching'). In this example, the participant would start with a 100-point credit, which is decimated to 40 after gambling yet losing on the first trial, resulting a losing 60 points

trial types that were more exogenous in nature, and two that were more endogenous. First, there were clearly favorable trials that always led participants to a gamble. This trial type was defined by a win proportion > 80% and a gain over 20 points. These trials were labeled GO trials. Second, there were trials that should always lead to a pass. This trial condition comprised trials with a gain of only 10 or 20 points, regardless of the proportional division of the colored bar. In these trials gambling was always disadvantageous as participants were certain of a 20 point gain when passing. Therefore, these trials were labeled NOGO trials. Both the GO and NOGO trials were considered to be exogenous trials as it is the stimulus that signals the participant on the most appropriate action. The third and fourth trial condition included trials with a proportional division between 50% and 75%, and a gain exceeding 20 points. These characteristics are not clearly pro gambling or pro inhibition. Instead it is not immediately clear to the participants which response should be given. The final decision in these trials will be guided by the interpretation of different kinds of information such as previous experiences, the gain or gain/loss ratio, the total score, or the moment during the task (e.g., at the beginning or near the end). Based on the chosen response, both a GAMBLE and PASS trial condition were defined. These trials are considered endogenous because the participants themselves decide on the most appropriate action without any cue from the stimulus. As such an identical trial sometimes leads to a gamble but other times to a pass depending on the decision of the participant.

All participants completed a practice run of 20 trials before entering the MR environment. During the fMRI session, all participants completed four runs of the task. Each run contained 50 gamble trials, resulting in a total of 200 trials for each participant.

fMRI data acquisition

Data were acquired on a 3.0-T MR system (Achieva, Philips, Best, the Netherlands) with an eight-channel phased-array head coil. Functional images were acquired using a T2*-weighted gradient echo (GE) echo planar imaging (EPI) sequence (TR = 1950 ms, TE = 33 ms; flip angle =90°; field of view = 240 × 240 mm^2; acquisition matrix = 80 × 78; acquired voxel size = 3 × 3.05 × 4.5 mm^3; 28 4.5 mm axial slices; EPI factor = 61; SENSE reduction factor = 1.4). For each run of the Gambling task 215 dynamic scans were acquired (total acquisition time = 7 min 13 s). For anatomical reference one high-resolution 3D-TFE T1-weighted structural scan was acquired for each subject (acquisition matrix = 256 × 182; field of view = 250 × 180 mm2; ip angle = 8°; TR = 9.725 ms; TE = 4.6 ms; acquired voxel size = 0.98 × 0.98 × 1 mm3; 230 1 mm coronal slices; SENSE reduction factor = 1.4). Stimuli were presented using the Eloquence fMRI system (InvivoMDE, MRI Devices Corporation Inc., Orlando, FL, USA).

Statistics

Confounding variables To establish whether maternal anxiety measured during weeks 23–31 and 32–40 of pregnancy, the postnatal maternal anxiety component score or birth weight, and/or the socioeconomic status of the parents should be included as covariates in the analyses, a prior correlation analysis was performed. This revealed no significant correlations between the dependent variables (gambling contrast value, totalscore) and maternal anxiety during the other pregnancy periods, postnatal maternal anxiety, birth weight and socioeconomic status nor between these confounding variables and

maternal anxiety measured during weeks 12–22 of pregnancy. Therefore, these covariates were not included in the analyses. The participants' intelligence score was also not included as the groups had been matched on intelligence test scores prior to inclusion (as indicated above).

Gambling behavioral analysis Due to its longitudinal design, the number of subjects included in the current phase of the study is limited. As there was no homogeneity in the variances of the dependent variables (assessed with Levene's Test), even after log-transforming these variables to improve normal distribution, we used randomization statistics. We decided to use this procedure instead of traditional parametric statistical tools to assess the effect of anxiety on the untransformed behavioral measures of the Gambling task because these methods are not bound to any underlying parametric assumption. The data for each subject in each of the two anxiety groups were entered in two vectors and the difference between the two means was calculated. After pooling both vectors, two new samples each the size of the previous vectors, were randomly drawn from the total sample and the difference between the means of these two new vectors was calculated. This was repeated 100,000 times, resulting in 100,000 differences. The difference between the original vectors was regarded significant when the probability of observing that difference was less than 5% when assessing the distribution of the differences calculated between the randomly drawn samples.

fMRI analyses Data were analyzed off-line using SPM5 software (Wellcome Department of Imaging Neuroscience, London, UK). All functional images were slice-time corrected and spatially realigned to the first volume of the first run. After coregistering the functional images to the anatomical image, they were spatially normalized to a custom-made T1 brain in the standard space of the Montreal Neurological Institute. The normalized functional images were resliced into 2 mm^3 isotropic voxels in MNI standard space and were spatially smoothed with a 6 mm full-width at half-maximum Gaussian kernel.

First, we wanted to identify prefrontal areas that are related to decision making upon presentation of the gambling stimulus. Identifying such task or condition specific regions will allow interpreting antenatal maternal anxiety related BOLD modulations in relation to the underlying decision-related cognitive processes. Prior to a second-level analysis assessing the effects of the included conditions, a first level analysis was performed on the data of each the nine men the low-average group. The GO, NOGO, GAMBLE and PASS trial conditions were modeled with a canonical hemodynamic response function (HRF), including time and dispersion derivatives. Next to the four decision trial conditions, negative, positive and neutral feedback were also modeled when present (i.e. some participants managed to finish runs without losing and thus also without receiving negative feedback). The six movement parameters of each session were included as covariates in the analysis. Note, that as these were all young adults, head movement was overall low in our sample, with an average maximum translation of 0.75 mm (SD = 1), and no difference in the maximum amount of head motion between the low-average and high anxiety groups ($t = -0.71$, $p = 0.48$).

Based on this analysis the percentage of signal change was calculated for each of the four decision conditions (GO, NOGO, GAMBLE, and PASS). These maps of the percentage of signal chance in each condition were then used in a second level 2-by-2 random-effects factorial analysis including the factors go/nogo and exogenous/endogenous. These factors were not independent because they comprised repeated measures from the same participants. The 2-by-2 design effectively consisted of four cells each including one of the four decision trial conditions of the Gambling task (go/exogenous: GO; nogo/exogenous: NOGO; go/endogenous: GAMBLE; nogo/exogenous: PASS). Significance for this analysis was assessed at false discovery rate (FDR) level with $p < .05$. Clusters were only assessed if they exceeded 50 voxels in size and were located anterior of central sulcus.

In a second analysis, we assessed the influence of antenatal maternal anxiety on the BOLD response of the participants using a fixed-effects analysis including all four runs of each of the 17 participants. The fixed-effects model, providing more degrees of freedom and statistical power, was chosen due to the limited number of subjects in both groups. As for the individual first level analyses described above, all four decision conditions and the three feedback conditions were modeled with a canonical HRF including time and dispersion derivatives. Again, the six movement parameters were included as covariates of no interest for each run. An F-contrast for comparing the low-average and high anxiety groups was calculated as a disjunction-contrast including effects of either condition. This means that the conditions were not pooled together but the calculated contrast included differences between the low-average and high anxiety groups in the GO or NOGO or GAMBLE or PASS condition. Significance threshold was set at an alpha level of .05 corrected for multiple comparisons (FWE). Only clusters including more than 50 significant voxels were interpreted. Next, significant clusters from this analysis were used as regions of interest (ROI) in separate 2-by-2 factorial ROI-based group analyses. For each ROI the percentage of signal change was calculated for each participant and compared in a repeated measures ANOVA, where participants were treated as a random factor. The model included group (low-average versus high anxiety) as between-subjects factor, and go/nogo and exogenous/endogenous as within-subjects factors. For these analyses a significance level of $p < .05$ was used.

Results

Gambling behavioral results

The participants in the high anxiety group performed significantly worse on the Gambling task compared to the participants of the low-average anxiety group. As can be seen in Fig. 2, there was a difference in the distribution of gambles/passes across trials between both anxiety groups. This distribution was quantified in a contrast measure defined as (M-S)/(S + M) where S is the proportion of gambles in the NOGO trials and M the proportion of gambles in all other trials. This contrast ranges between −1 (only gambles in the NOGO trials) and 1 (only gambles in the other trials), with 0 indicating equal percentages of gambles in both trial categories. The scatterplot in Fig. 2 clearly shows that the contrast was close to 1 for the participants in the low-average anxiety group (M = 0.96, SD = 0.02), and significantly higher compared to the contrast for the high anxiety group (M = 0.88, SD = 0.14) ($p < .03$).

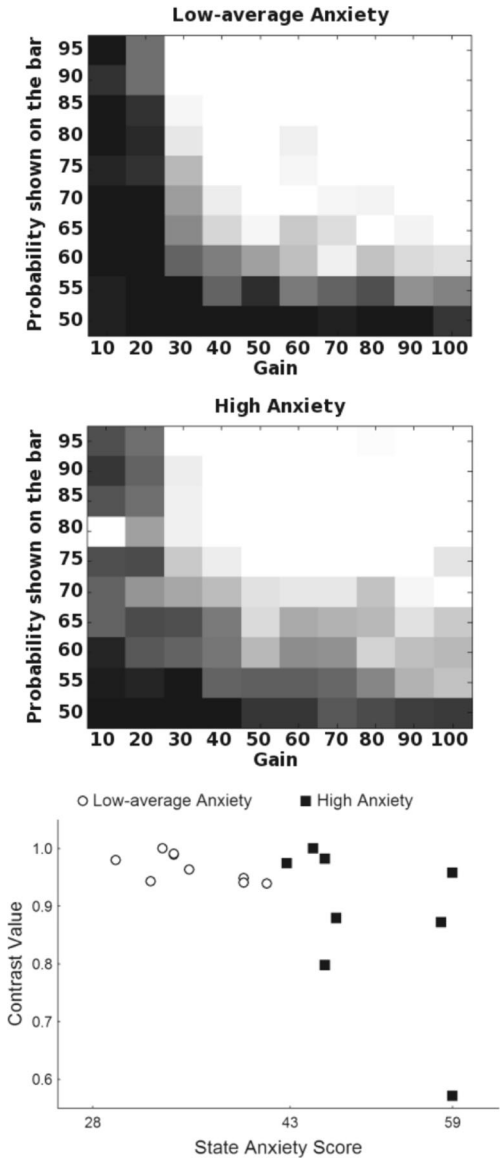

Fig. 2 Percentage of gambles made in the different trials of the Gambling paradigm for the low-average and high anxiety group. Darker squares indicate a higher percentage of inhibitions (black = 100% pass), lighter squares indicate a higher percentage of gambles (white = 100% gamble). Trials are ordered according to the proportional division of the stimulus bar (Y-axis) and the amount of points that could be won (X-axis). The bottom graph shows the contrast values calculated based on the behavioral diagrams of each participant in relation to the maternal state anxiety score at 12–22 weeks of pregnancy

Next to a difference in this gambling contrast the participants in the high anxiety group also earned significantly less points across the four sessions compared to the participants in the low-average group (low-average: M = 7953, SD = 494.22; high: M = 6735, SD = 1460.3; $p < .02$). There was no effect of anxiety on the reaction time or the standard deviation of the reaction time.

fMRI results

Effects of condition in the low-average anxiety group

Significant regions of activation for the effects of condition in the participants of the low-average anxiety group are shown in Table 1. Five prefrontal clusters showed significant differences when assessing the effect of go (including the GO and GAMBLE trials) versus nogo (including the NOGO and PASS trials) decision trials. Clusters in left middle frontal gyrus and right superior frontal sulcus showed a go < nogo effect. In contrast, anterior cingulate cortex (ACC), left insula and left inferior precentral sulcus showed a go > nogo effect. As expected, the strongest go > nogo effects were observed in primary motor cortex.

A number of clusters showed significant differences related to the exogenous (GO and NOGO) and endogenous (GAMBLE and PASS) trials. These clusters are shown in Fig. 3. Except for one cluster in left middle frontal gyrus all clusters showed greater activations in the endogenous compared to the exogenous trials. This effect included clusters in right dorsal ACC, right inferior frontal sulcus, right inferior frontal junction, right inferior precentral sulcus, right superior frontal sulcus, and left operculum. There were no clusters that showed a go/nogo by exogenous/endogenous interaction.

Effects of maternal anxiety during weeks 12–22 of pregnancy

Comparing the BOLD response of the participants in the low-average anxiety group with that of the participants in the high anxiety group yielded 15 significant clusters in prefrontal cortex (see Table 2). Investigating the percentage of signal change in each of these ROIs, revealed that the relationship

Table 1 Regions activated during the decision phase of the Gambling paradigm in the adolescents of the low-average anxiety group

		Side	x	y	z	t-value	n voxels
Main effect go/nogo							
go > nogo							
Inferior precentral sulcus		L	−60	6	30	5.21	82
Insula		L	−38	2	12	5.70	228
ACC		R	4	−2	54	6.63	824
		R	2	−16	54	5.55	
		R	6	4	44	5.02	
go < nogo							
Middle frontal gyrus		L	−36	16	56	−4.71	74
Superior frontal gyrus		R	22	24	58	−4.86	56
Main effect of exogenous/endogenous							
Exogenous > endogenous							
a	Middle frontal gyrus	L	−30	32	48	6.07	154
Exogenous < endogenous							
b	Superior frontal sulcus	R	28	4	58	−6.27	232
c	Inferior precentral sulcus	R	54	12	26	−4.69	91
d	Inferior frontal junction	R	38	22	36	−4.39	74
e	ACC	R	6	20	48	−9.84	1791
		R	10	30	34	−7.92	
		R	0	18	54	−6.39	
f	operculum	L	−30	28	0	−5.60	117
g	operculum	R	32	22	4	−8.69	395
h	Inferior frontal sulcus	R	36	32	26	−6.16	237

Activations are assessed at false discovery rate (FDR), $p < .05$

between the BOLD response and the level of antenatal maternal anxiety differed depending on the assessed ROI.

First, there were six ROIs that showed a main effect of anxiety, without any interactions between anxiety and the within-subject variables. These ROIs could be further divided based on the difference between both anxiety groups. Four ROIs showed activations in the participants of the low-average anxiety group, but not in the participants of the high anxiety group (see Fig. 4). These included left inferior precentral sulcus ($F(1,15) = 8.06$; $p < .01$), left inferior frontal gyrus pars opercularis ($F(1,15) = 9.5$; $p < .01$), left middle frontal gyrus superior ($F(1,15) = 11.5$; $p < .01$) and a ROI in ACC ($F(1,15) = 5.8$; $p < .03$). In contrast, as shown in Fig. 5, left superior frontal junction ($F(1,15) = 12.8$; $p < .01$) and a cluster in left inferior frontal sulcus ($F(1,15) = 6.99$; $p < .02$) showed no activation in the low-average anxiety group, but positive activations in the high anxiety group. A similar effect was observed in a cluster in left inferior frontal gyrus pars triangularis ($F(1,15) = 7.31$; $p < .02$). Here the participants of the high anxiety group showed negative activations in absence of activations for the low-average anxiety group. This cluster also showed a significant anxiety by exogenous/endogenous interaction ($F(1,15) = 4.96$; $p < .05$), due to a positive activation observed in activation for the PASS trials of the low-average anxiety group.

Second, Fig. 6 shows six ROIs where the ANOVA yielded an anxiety by exogenous/ endogenous interaction. Again these could be subdivided. In four ROIs an exogenous/ endogenous modulation could be observed in the activations of the participants of the low-average anxiety group. However, this modulation was absent in the participants of the high anxiety group. These ROIs included right inferior frontal junction ($F(1,15) = 11.27$; $p < .01$), right middle frontal gyrus inferior ($F(1,15) = 16.94$; $p < .001$), and a bilateral ROI in inferior precentral sulcus (left: $F(1,15) = 13.18$; $p < .01$; right: $F(1,15) = 6.8$; $p < .02$). Next to these four clusters there were two clusters that showed an exogenous/endogenous effect in the participants of both anxiety groups. However, the difference in activation between the participants in the low-average anxiety group and those in the high anxiety group was larger in the endogenous trials compared to the difference between both groups in the exogenous trials. These clusters were found in left superior frontal junction ($F(1,15) = 5.26$; $p < .04$) and left middle frontal gyrus anterior ($F(1,15) = 6.8$; $p < .02$).

Third, one cluster yielded an anxiety by go/nogo interaction. This cluster in right superior frontal junction ($F(1,15) =$

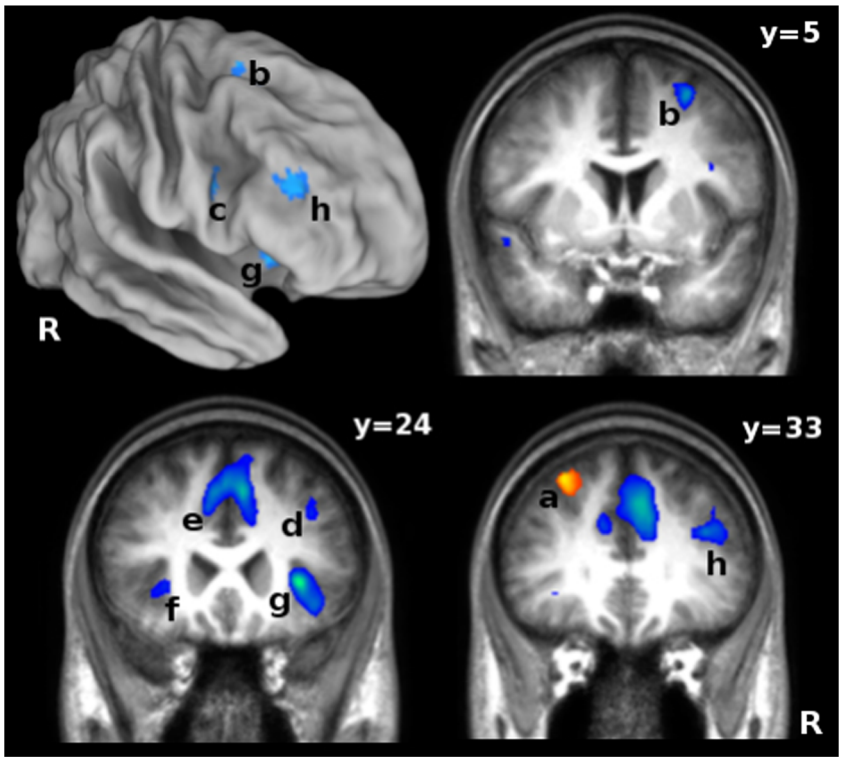

Fig. 3 Activation maps of the exogenous/endogenous manipulation in the Gambling paradigm for the participants in the low-average anxiety group. Left top shows an overview of the activations plotted on the right hemisphere of the PALS-B12 atlas using CARET software (http://brainmap.wustl.edu/caret, Van Essen 2002). Coronal slices show activations plotted on the mean T1 image of the nine participants of the low-average anxiety group. Maps are thresholded at FDR $p < .05$, $t > 3.59$. Red colors indicate exogenous > endogenous activations, blue indicates endogenous > exogenous activations. Letters indicate clusters as shown in Table 1

11.68; $p < .01$) was active only in the go (GO and GAMBLE) trials of the participants of the low-average group.

Fourth, there was one cluster that yielded a 3-way anxiety by go/nogo by exogenous/endogenous interaction. However, it is not clear what caused the effect in this left superior precentral sulcus cluster ($F(1,15) = 6.42$; $p < .02$), as post-hoc comparisons did not yield significant differences between both anxiety groups in each of the four conditions. Borderline differences were observed in the GO ($p = .06$) and PASS ($p = .08$) condition.

In summary, we found clusters that were active only in the participants of the low-average anxiety group ($n = 4$), clusters that were active only in the participants of the high anxiety group ($n = 3$), clusters that showed an exogenous/endogenous modulation only in the participants of the low-average anxiety group (n = 4), clusters where the difference between both anxiety groups was larger for endogenous trials ($n = 2$), one cluster that was active only in the go trials of participants in the low-average anxiety group and finally one cluster showing mixed results. It is important to note that most clusters were found in the left hemisphere, except for the clusters showing an exogenous/endogenous modulation in the participants of the low-average group but not in the participants of the high anxiety group.

There was no overlap between the clusters that showed anxiety related modulations and the clusters that were activated in the participants of the low-average anxiety group by the go/nogo condition manipulation. In contrast, there were four clusters, showing more activity in endogenous compared to exogenous trail conditions in the low-average anxiety group, that overlapped with clusters that were also significant in the comparison between the two anxiety groups. These clusters were observed in ACC, inferior frontal sulcus, inferior frontal junction and inferior precentral sulcus. All were lateralized to the right hemisphere.

Discussion

The effect of maternal anxiety during pregnancy on the BOLD response in 20-year-old men

The BOLD response of 20-year-old men measured during decision making in a Gambling paradigm was found to be related to the level of anxiety reported by their mothers during weeks 12–22 of pregnancy. We observed a heterogeneous pattern of differences in brain activation related to antenatal maternal anxiety in a number of areas in prefrontal cortex. Some of these clusters were also modulated by the exogenous/endogenous cognitive control manipulation in the Gambling paradigm but only in the participants of the low-average anxiety group. Opposed to our previous hypothesis that was based on purely neurocognitive behavioral results, the BOLD modulations that yielded a relationship with antenatal maternal anxiety were not confined to orbitofrontal cortex. There were no effects of antenatal maternal anxiety on brain activity related to mere response inhibition, nor in brain areas commonly involved in successful inhibition.

Table 2 Regions that are activated during the decision phase of the Gambling paradigm when comparing the adolescents of the low-average anxiety group to the adolescents of the high anxiety group

		Side	x	y	z	F-value	n voxels
Main effect of anxiety							
1	Inferior precentral sulcus, superior	L	−37	8	50	8.66	561
2	Inferior frontal gyrus, pars opercularis	L	−56	16	16	9.28	300
3	Middle frontal gyrus, superior	L	−32	20	52	6.34	561
4	ACC	R	8	34	42	7.04	58
5	Superior frontal junction	L	−22	6	58	9.50	128
6	Inferior frontal sulcus	L	−36	10	32	10.26	561
7	Inferior frontal gyrus, pars triangularis	L	−48	40	8	6.43	98
Anxiety by exogenous/endogenous interaction							
8	Superior frontal junction	L	−28	−10	68	13.92	188
9	Middle frontal gyrus, anterior	L	−24	56	26	8.62	197
10	Inferior precentral sulcus	L	−52	12	34	8.85	113
11	Inferior precentral sulcus	R	58	10	30	10.43	606
12	Inferior frontal junction	R	44	20	40	6.76	606
13	Middle frontal gyrus, inferior	R	40	38	20	10.70	606
Anxiety by go/nogo interaction							
14	Superior frontal junction	R	32	−8	66	7.39	86
Anxiety by go/nogo by exogenous/endogenous interaction							
15	Superior precentral sulcus	L	−48	0	38	12.75	130

Activations are assessed at $p < .05$ corrected for multiple comparisons (FWE)

Importantly, these findings confirm our previous exogenous cognitive control results as well as our ERP results in the same sample, where no behavioral, nor brain wave differences were found in simple go/nogo conditions.

As hypothesized, the exogenous/endogenous manipulation in the Gambling task yielded the most important modulations related to antenatal maternal anxiety. In four prefrontal clusters, including the right inferior frontal junction, an anxiety by exogenous/endogenous interaction indicated that the participants in the low-average anxiety group showed more positive activity in the endogenous compared to the exogenous trials, while such modulation was absent in the participants of the high anxiety group. Because these clusters were directly related to the endogenous aspect of the task, as revealed by the separate exogenous/endogenous contrast calculated for the participants of the low-average anxiety group only, it is likely that these clusters are relevant for the implementation of endogenous cognitive control. These results are in line with other studies associating inferior frontal junction with endogenous cognitive control in gambling (Meder et al. 2016; Vallesi et al. 2015; Zysset et al. 2006) and task-switching paradigms (Brass et al. 2005; Forstmann et al. 2005). More importantly, the overlap between these clusters and clusters indicating a difference in brain activity related to antenatal maternal anxiety confirms our previous hypothesis regarding an association between antenatal maternal anxiety and endogenous cognitive control (Mennes et al. 2006; Van den Bergh et al. 2005a, 2006). The observed differences in activation suggest that modulations in brain activity typically related to endogenous cognitive control are not present in the participants of the high anxiety group. Therefore, they suggest less efficient implementation of endogenous cognitive control in the offspring of mothers experiencing high levels of anxiety during their pregnancy.

A number of prefrontal clusters yielded a main effect of anxiety. Half of these clusters showed this effect due to significant deactivation in the participants of the low-average anxiety group compared to no activity at all in the high anxiety group. Deactivation of prefrontal regions including the posterior insula during cognitively demanding tasks is associated with an increase in the need for focused attention towards the specific task demands (Gusnard and Raichle 2001; Lawrence

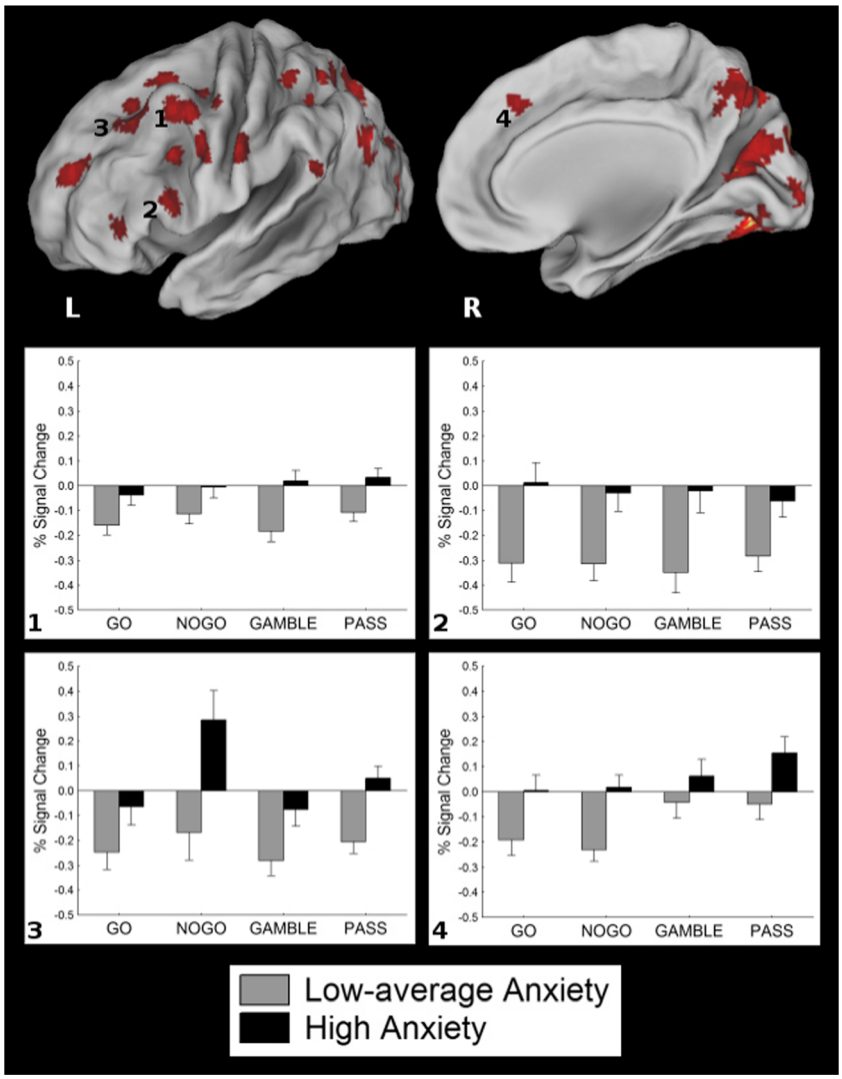

Fig. 4 Overview of clusters showing more deactivation in the participants of the low-average anxiety group. Bar plots show the percentage of signal change in the designated clusters for each of the four decision conditions of the Gambling paradigm. Activated clusters are plotted on the left and right hemisphere of the PALS-B12 atlas using CARET software (http://brainmap.wustl.edu/caret, Van Essen 2002). Activations are thresholded at $p < .05$ corrected for multiple comparisons (FWE), $F > 4.39$. Numbers indicate clusters as shown in Table 2

et al. 2003) or to an optimization of performance by minimizing interference from task-irrelevant areas (Tomasi et al. 2006). In line with this, Hester et al. (2004) have found that unsuccessful inhibition trials were associated with a failure to deactivate the insula, suggesting that a failure in attention regulation was the cause for unsuccessful performance. In the present study, the insula was equally deactivated across exogenous and endogenous conditions in the participants of the low-average anxiety group, suggesting task-related, but not condition-specific deactivation. In contrast, the other clusters that yielded a main effect of anxiety showed no activation in the participants of the low-average anxiety group compared to either clearly positive or negative activations for the participants of the high anxiety group, suggesting that these participants effectively use other areas of prefrontal cortex during decision making compared to the participants in the low-average anxiety group. This is consistent with findings in children with ADHD showing that these children use a more diffuse network of prefrontal regions compared to control children (Durston et al. 2003). Similar observations were made in adults with ADHD, even after normalization of their behavior through medication (Schweitzer et al. 2004).

Taken together these results indicate that there is a relationship between the level of anxiety experienced by a mother during pregnancy and deficits in endogenous cognitive control and its associated functional brain activity in the prefrontal cortex of her offspring, while no deficits were seen in exogenous cognitive control and correlated prefrontal functional brain activity. Participants of mothers reporting high levels of anxiety during weeks 12–22 of their pregnancy seem to show discrepant activation in areas that are recruited by participants of mothers reporting low to average levels of anxiety. In addition, the participants in the high anxiety group recruited areas that were not active in the participants of the low-average anxiety group. The suboptimal cognitive control results for this group suggest that the network recruited by participants in the high anxiety group is less efficient compared to the network of areas used by participants in the low-average

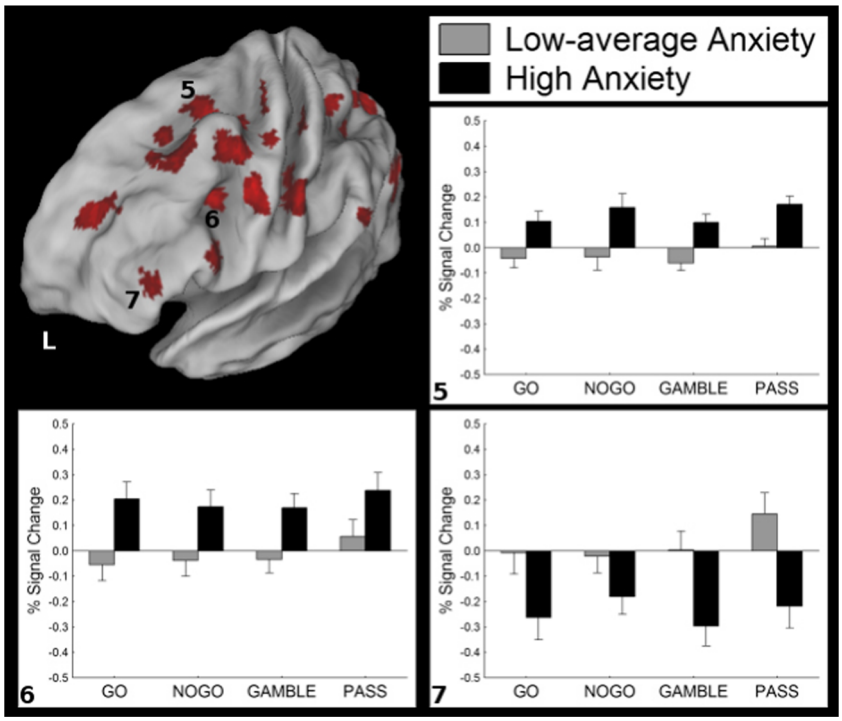

Fig. 5 Overview of clusters showing activation in the participants of the high anxiety group but not in the participants of the low-average anxiety group. Bar plots show the percentage of signal change in the designated clusters for each of the four decision conditions of the Gambling paradigm. Activated clusters are plotted on the left hemisphere of the PALS-B12 atlas using CARET software (http://brainmap.wustl.edu/caret, Van Essen 2002). Activations are thresholded at $p < .05$ corrected for multiple comparisons (FWE), $F > 4.39$. Numbers indicate clusters as shown in Table 2

anxiety group. Especially areas that are important for the implementation of endogenous cognitive control were not modulated by this type of cognitive control in the participants of the high anxiety group.

It is possible that a difference in maturation underlies the observed differences in activation between the participants in the low-average and high anxiety groups. The prefrontal cortex still undergoes developmental changes during adolescence (Paus 2005) and even adulthood (Billiet et al. 2015). Imaging studies on the development of cognitive control provide evidence showing also functional changes in the involved prefrontal circuitry with maturation (Bunge et al. 2002; Durston et al. 2002). However, although the majority of areas that were related to antenatal maternal anxiety showed less activation in the participants of the high anxiety group, we also found areas showing increased activation for this group. This suggests that the participants in the high anxiety group potentially compensate for the less efficient activation of certain areas by recruiting extra areas that were not recruited by the participants in the low-average anxiety group.

To the best of our knowledge, this is the first study to directly associate maternal anxiety during pregnancy with task-related functional magnetic resonance imaging (fMRI) in adult offspring, using a prospective design. This enables us to link a specific aspect of adult *behavior* (i.e., endogenous cognitive control) as well as its associated *brain* activation (i.e., the BOLD response), to antenatal exposure to maternal anxiety. Although we cannot directly compare our results to those of other task-related fMRI studies, they do in general correspond to those of studies showing that MPDP is associated with changes in prefrontal functional connectivity as measured with fMRI, be it that the latter studies involved only infants (e.g., Posner et al. 2016; Qiu et al. 2015a).

Study limitations

It is possible that the present effects are due to genetic differences interacting with antenatal anxiety. We cannot disentangle genetic effects versus environmental effects since we lack information on genetic profiles of the participants and their mothers and fathers. If genetic effects would be vital, a significant correlation between postnatal maternal anxiety and the dependent variables should have been found; however, this was not the case. Also, none of DSM oriented scales, internalizing and externalizing problem derived from the parental ASR scales were significantly different between the two groups. If one sees these scales as proxy measures of the genetic endowment for psychopathology, it is accordingly unlikely that the present effects were mainly due to genetic differences. A second limitation for our conclusions is the limited number of participants we were able to include. Therefore, our results should be considered preliminary and further validation in larger samples is needed. However, to mitigate this concern, we had chosen a fixed-effects analysis for comparing the brain activity of the participants of both anxiety groups. Although providing valid results for the investigated sample this type of analysis hampers possible interpretations with respect to the total population; i.e., while the internal validity is sound, the external validity of our results might be limited. The smaller sample size also increases the chance for type II

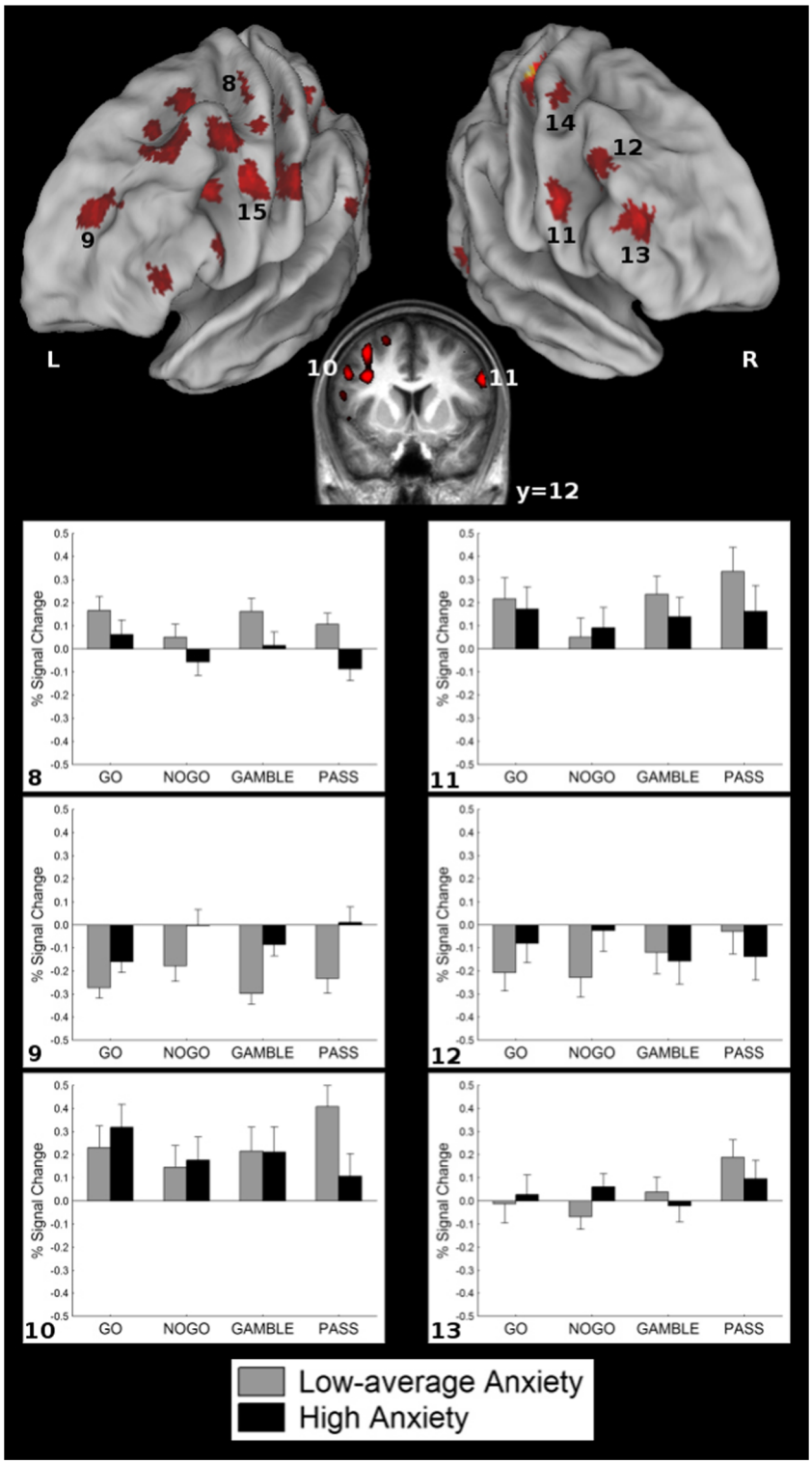

Fig. 6 Overview of clusters showing a group by exogenous/endogenous interaction. Bar plots show the percentage of signal change in the designated clusters for each of the four decision conditions of the Gambling paradigm. Bar plots are not shown for clusters 14 and 15. Cluster 14 showed a group by go/nogo interaction, cluster 15 showed a group by go/nogo by exogenous/− endogenous interaction. Activated clusters are plotted on the left and right hemisphere of the PALS-B12 atlas using CARET software (http://brainmap.wustl.edu/caret, Van Essen 2002). Activations are thresholded at $p < .05$ corrected for multiple comparisons (FWE), $F > 4.39$. Numbers indicate clusters as shown in Table 2

errors, indicating that significant differences were missed. This could for instance be the case for activations in orbitofrontal cortex. However, it should be noted that due to the longitudinal design of the study it was impossible to include new participants as we would have no access to data on the level of anxiety experienced by the mothers gathered during their pregnancy. The longitudinal design is on the other hand, also an obvious strength of the current study. Within the same sample, we found evidence for an impairment in endogenous cognitive control related to the level of exposure to antenatal maternal anxiety at different moments during development and using different techniques (Mennes et al. 2006,

2009; Van den Bergh et al. 2005a, 2006). Finally, the choice of our cognitive tasks has a tradeoff. In the gambling tasks (and cognitive control tasks used in prior studies in this cohort), the best performance was to be achieved by persons scoring high on endogenous cognitive control. We know that the high anxious group had no worse performance on exogenous cognitive tasks, but only the use of genuine exogenous cognitive tasks (where the best performance is to be achieved by persons who score high on exogenous cognitive control) could have revealed whether the high anxious group in fact excels in this kind of tasks and what the associated functional brain networks are. If a proneness to react promptly to external signals was to be found, this could be a strength (e.g., to act adaptive in a dangerous or stressful environment, for which offspring exposed to MPDP may have been 'programmed'), but also a risk factor (e.g., to develop an anxiety disorder). The final outcome depends on whether or not vigilance becomes an overgeneralized reaction, i.e., one that extends to safe environments (Van den Bergh 2016; van den van den Heuvel et al. 2017). Studies focusing on offspring *potential* strengths are lacking. However, they are important in the DO(B)HaD field since results of these studies may lead to interventions that focus on biological mechanisms and capitalize on strengths and on enhancing resilience rather than on reducing symptoms (Lewis et al. 2014; Schlotz and Phillips 2009).

The past and future of our cohort: on neurodevelopmental disorders and underlying mechanisms

Animal models, natural experiments and other empirical research in humans have shown that next to the influence of genetic factors (Stein et al. 2014), maternal distress during pregnancy induces changes in the placenta, in offspring stress and immune system, telomere length, microbiome, and brain developmental processes, most probably by inducing changes in epigenetic mechanisms, (Christian et al. 2009, 2010, Christian 2014; Hanamsagar and Bilbo 2016; Knuesel et al. 2014; Labouesse et al. 2015; Leff-Gelman et al. 2016; Rakers et al. 2017; Stein et al. 2014; Van den Bergh et al. 2017; Veru et al. 2014, 2015). We plan to study some alterations in telomere length, epigenetics, and the immune system in a future wave of our cohort. We will again focus on the intermediate level and e.g. examine changes in brain structural maturation and whether there is evidence for an association between MPDP and offspring altered white mattermicro-structure and altered brain functional connectivity involving attentional networks.

In previous waves of our longitudinal studies we showed a link between MPDP and offspring neurodevelopmental disorders such as ADHD (Van den Bergh and Marcoen 2004; Van den Bergh et al. 2006) and depression (Van den Bergh et al. 2008). In the current study the ASR completed by 14 participants and the ACBL completed by their mothers and fathers revealed no group differences. The lack of significant differences for ADHD measures between the two groups may be due to too low statistical power or may indicate that the participants of the high anxiety group no longer show behavior typically seen in persons with ADHD. It is tempting to hypothesize that the higher fetal motor activity observed at 36–38 weeks of gestation in this cohort may be seen as a precursor of hyperactive and impulsive behavior at the age of 8–9 (Van den Bergh and Marcoen 2004) and 14–15 years (Van den Bergh et al. 2006), and that fetal brain imaging modalities would be able to already at that age (or even earlier; see van den Heuvel and Thomason 2016) detect alterations in brain structure and function associated with this behavior. In larger samples, studies of brain alterations in the aftermath of exposure to MPDP should also aim at revealing compensatory mechanisms. These mechanisms may explain part of the phenotypical heterogeneity seen in many neurodevelopmental disorders and which are considered in the 'multiple causal pathways model on the etiology of ADHD' (Faraone et al. 2015).

Conclusion

The current results show a relationship between functional brain activity during task performance, measured with fMRI, and the level of anxiety experienced by a mother during weeks 12–22 of her pregnancy, in a study with a prospective design. The modulation of activity in areas that are important for the implementation of endogenous cognitive control provides compelling support for the hypothesis that high levels of maternal anxiety during pregnancy are related to a deficit in endogenous cognitive control. These results are consistent with those seen in the 17-year-olds, involving EEG measures. We therefore conclude that both, a deficit in endogenous cognitive control and the associated functional brain alterations are to be seen as markers of exposure to MPDP which are persistent until at least the age of 20. Due to the small sample size our results are to be considered as preliminary; they need further confirmation in larger samples. The current results also suggest that the maturation of prefrontal cortex and functional brain networks should receive special interest in future DO(B)HaD research. Further research into the mechanisms underlying the observed relationship is needed. Results of these studies may then lead to a better understanding of offspring enhanced susceptibility to disorders and enable tailoring interventions to the specific difficulties ánd strengths of the affected offspring. Today, remedial programs for neurodevelopmental disorders such as ADHD mainly target symptoms (Faraone et al. 2015; Hinshaw 2018). However, designing and providing interventions that reduce anxiety and enhance resilience of the pregnant mother and/or also

target biological processes that have predisposed the offspring to developmental disorders may be more effective since they may improve offspring motor, cognitive and affective outcome and resilience right from the start. This kind of preventive mental health care will be crucial in future public health policy all over the world (e.g., Bauer et al. 2016).

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Compliance with ethical standards

Disclosure of potential conflicts of interest The authors declare that they have no conflict of interest.

Research involving human participants The local ethical committee for experiments on human subjects approved the study. The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Informed consent All participants were clearly informed about the scanning procedures and gave their written informed consent.

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